IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT	: Jackowski et al.
INVENTION	: **Fibronectin Biopolymer Markers Indicative of Type II Diabetes**
SERIAL NUMBER	: 09/991,796
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EXAMINER	: Chernyshev, Olga N.
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APPLICANT'S BRIEF IN ACCORDANCE WITH 37 CFR 1.192(c)

This is an appeal of the final rejection of Claim 1 by Examiner Olga N. Chernyshev of the United States Patent and Trademark Office.

Respectfully submitted,

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I. REAL PARTY IN INTEREST

The real party in interest is the assignee, Nanogen, Inc.

II. RELATED APPEALS AND INTERFERENCES

A similar appeal has also been filed by Appellant in US Application Serial Number 09/994,909 (attorney docket number 2132.090), filed on November 23, 2001, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. STATUS OF CLAIMS

Claims 1 and 39-46 are pending in the instant application. Claims 39-46 are withdrawn from consideration on the merits based upon a restriction requirement mailed January 23, 2003. Claims 2-38 are cancelled. Claim 1 is under examination. The final rejection of claim 1 under both 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is appealed.

IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Rejection mailed on March 16, 2006.

V. SUMMARY OF INVENTION

The invention defined in the claim under appeal, claim 1, is drawn to isolated peptide fragments of fibronectin precursor protein having the sequences of SEQ ID NOS:1 and 4 which are determined to be linked to Type II diabetes from their differential expression in Type II diabetes versus normal controls. *See* Figures 1-4 of the specification as originally filed.

It is another objective of the instant invention to evaluate samples containing a plurality of biopolymers for the presence of disease-specific biopolymer marker sequences (disease-specific markers) which evidence a link to at least one specific disease state. *See* the instant specification as originally filed at page 35, lines 14-18.

As a result of these procedures, the disease-specific markers, namely Fibronectin Precursors, having a molecular weight of about 1629.94 daltons and a sequence of SEQ ID NO:1, a molecular weight of about 1927.0442 daltons and a sequence of SEQ ID NO:2, a molecular weight of about 2127 daltons and a sequence of SEQ ID NO:3, a molecular weight of about 1629.87 daltons and a sequence of SEQ ID NO:4, a molecular weight of about 1913.08 daltons and a sequence of SEQ ID NO:5, and a molecular weight of about 1682.96 daltons having a sequence of SEQ ID NO:6 related to Type II diabetes were found. *See* page 46, line 14 to page 47, line 2 of the specification as originally filed, presented herein as amended on September 22, 2003.

VI. ISSUES

A. Whether Claim 1 is Unpatentable under 35 U.S.C. § 101 as Having No Specific and Substantial Credible Utility

   1. Whether the Examiner Made a *Prima Facie* Showing that the Invention Lacks a Specific and Substantial Utility

   2. Whether the Examiner Properly Held that Applicant's Asserted Utility Lacks Credibility

B. Whether Claim 1 is Unpatentable under 35 U.S.C. § 112, First Paragraph as Being Based on a Nonenabling Disclosure

1. Whether the Examiner Properly Evaluated the Application for Enablement.

VII. GROUPING OF CLAIMS

Claim 1 is the only claim currently under appeal.

VIII. ARGUMENT

A. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 101

1. The Examiner Has Failed to Make a Prima Facie Showing that the Invention Lacks A Specific And Substantial Utility.

Claim 1, as presented in the Response filed on February 9, 2006, stands finally rejected (Final Rejection dated March 16, 2006) under 35 U.S.C. § 101.

The Examiner has maintained the rejection under 35 U.S.C. § 101, finding that the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. Applicants respectfully request reconsideration of the rejection as Applicants have established a specific and substantial credible utility for the claimed invention.

As set forth below, Applicants have disclosed an invention having specific, substantial, well-established and credible utility by showing an invention that is useful to the public as disclosed in its current form, rather than at some future date after further research, as peptide markers linked to Type II diabetes. Furthermore, Applicants have supported this utility with data specifically directed to patients having Type II diabetes.

The novelty of the biopolymer markers designated as SEQ ID NOS: 1 and 4 has been established during examination. The alleged lack of a disclosed specific and substantial credible utility has thus far prevented Claim 1 from being deemed patentable.

The standard for satisfying the requirements for utility under 35 U.S.C. § 101 is not particularly high. In most cases, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy 35 U.S.C. § 101. *See* In re Langer, 503 F.2d 1380, 1391, 183 USPQ 297 (CCPA 1974); MPEP § 2107.02(III)(A). In other words, the Office is correct to presume that a statement of utility made by an applicant is true.

Accordingly, the Examiner should presume that the claimed peptides (SEQ ID NOS:1 and 4) are useful as markers for Type II diabetes based upon Applicants' showing in Figures 1 and 3 that the peptides are linked to Type II diabetes by their differential expression in Type II diabetes patients as compared to healthy control patients.

A "specific utility" refers to a utility that is well-defined, particular and specific to the subject matter claimed. Vague expressions such as "a compound has useful biological activity" or "biological properties" are meaningless. In re Fisher, 421 F.3d 1365, 1371, 76 USPQ2d 1225 (Fed. Cir. 2005); In re Kirk, 376 F.2d 936, 941, 153 USPQ 48 (CCPA 1967); MPEP § 2107.01. For example, a general statement indicating that a marker is useful for diagnostics, such as diagnosing a disease, would be insufficient, absent a disclosure of what disease and/or condition could be diagnosed. In contrast, a statement of diagnostic utility, such as diagnosing Type II diabetes, would be sufficient to identify a specific utility for the invention. Thus, Applicants' statement of utility regarding the use of the claimed peptide as a marker for Type II diabetes constitutes a specific utility since the claimed peptide is linked to the specific condition of Type II diabetes.

It is well known that pathological changes in an organism are reflected by changes observed in the serum protein pattern. For example, proteins that undergo a

change in expression (from the normal) are often indicative of disease. A diagnosis may be predicted based upon the similarity of unknown sample pattern to known pattern of disease. Mass spectrometry is a tool used to establish serum protein patterns. *See* page 11 of the Response filed on February 9, 2006.

Generally proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are often first subjected to separation by polyacrylamide gel electrophoresis. Upon electrophoresis, the proteins contained in the sample separate into bands in specific areas of the gel according to weight and charge. The separated protein bands which are observed and deemed to be different between two comparable states (for example, disease state vs. normal state) are excised from the gel and subjected to further fragmentation by enzymes. The resulting peptides are then collected and purified by chromatography prior to identification by mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The mass spectral profiles generated are composed of parts of the original protein and can be used to identify this protein. *See* page 38, line 10 to page 40, line 20 of the specification.

In order for a rejection under 35 U.S.C. § 101 to be appropriate, the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention. In re Cortright, 165 F.3d 1353, 1355, 49 USPQ2d 1464 (Fed. Cir. 1999).

It is respectfully submitted that the "link to Type II diabetes" asserted by Applicants was elucidated under real-world conditions according to the methodology set forth in the following steps:

I. isolating peptides from body fluid samples obtained from two groups of patients; a) one group known to suffer from Type II diabetes; and b) a group of controls (healthy in regard to Type II diabetes);

II. carrying out the protocols disclosed in the specification (pages 37-47);

III. comparing the expression pattern of protein bands from the two groups of patients as evidenced in gels (such as that shown in Figures 1 and 3);

IV. subjecting the noted expression pattern to the criteria as disclosed in the specification at page 11, lines 9-20;

V. selecting and excising bands that are differentially expressed between the two groups, and, submitting the peptides present within the excised bands for further fragmentation and purification followed by sequence identification by mass spectrometry.

The Applicants, using the above-described methodology in a real-world environment, thereby elucidated and identified SEQ ID NOS:1 and 4 as fragments of fibronectin precursor protein found in healthy, control patients but absent in patients having Type II diabetes, thus establishing the instantly claimed link to Type II diabetes evidenced by the observed differential expression.

The characteristic mass spectral profiles indicative of the claimed peptides are disclosed in Figures 2 and 4 (SEQ ID NO:1 in Figure 2 and SEQ ID NO:4 in Figure 4). Mass spectral profiles are reproducible and are typically published to provide established expression patterns for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profiles (shown in Figures 2 and 4) provided in the instant specification as references for comparing with mass spectral profiles of

peptides obtained from an unknown sample to test the unknown sample for a link to Type II diabetes through comparison of expression patterns, thereby demonstrating that the specification discloses a specific and substantial utility for the claimed peptides. These mass spectral profiles are a showing of factual evidence that the claimed peptides could be used as markers for Type II diabetes. Thus, the instant specification provides data (gels shown in Figures 1 and 3 and the mass spectral profiles shown in Figures 2 and 4) supporting the desired results of the claimed invention; i.e. biopolymer markers for Type II diabetes.

Accordingly, Applicants respectfully submit that the Examiner has failed to adhere to the precedent set in Cortright by failing to establish that there is a complete absence of data supporting the statements which sets forth the desired results of the claimed invention.

The Examiner asserts that one skilled in the art readily understands that in order to use the claimed peptides as markers for Type II diabetes, a point of reference that is critical for diagnosis with respect to the levels of differential expression of the claimed peptides must be disclosed. The Examiner then concludes that in the absence of this critical information, it is unclear as to how one of skill in the art can reasonably determine if the claimed peptides can be used as diagnostic markers for Type II diabetes and thus, one of skill in the art would have to resort to a substantial amount of further experimentation in order to practice Applicants' invention. *See* page 8 of the Final Office Action mailed on March 16, 2006. However, with regard to providing a link to Type II diabetes as is instantly claimed, it is well settled that an applicant is not required to

provide evidence of an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980); MPEP § 2107.02.

Thus, Applicants respectfully submit that providing a point of reference that is critical for diagnosis with respect to the levels of differential expression of the claimed peptides is not necessary to establish credibility of the asserted use for the claimed peptides as markers for Type II diabetes. Accordingly, Applicants respectfully submit that the Examiner's requirement for such information is improper.

A "substantial utility" is a utility that defines a "real-world" use. MPEP §2107.01(I). "Substantial utility" refers to a significant and presently-available benefit to the public. An application must show an invention that is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. "In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." Fisher, 421 F.3d at 1368, *citing* Nelson, 626 F.2d at 856.

In the context of an evaluation of substantial utility, the phrase "immediate benefit to the public" must not be interpreted to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Brenner v. Manson, 383 U.S. 519, 534-535, 148 USPQ 689 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". MPEP § 2107.01(I).

Additionally, care must be given not to find a lack of specific and substantial utility based upon the setting in which the invention is to be used. This is particularly

important in biotechnology; for example, during examination of inventions to be used in a research or a laboratory setting. As the Federal Circuit noted:

> "An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact 'useful' in a patent sense. [The PTO] must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm." Fisher, 421 F.3d at 1372, *citing* MPEP § 2107.01(I).

Many research tools such as gas chromatographs, screening assays and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g. they are useful in analyzing compounds). MPEP § 2107.01(I).

Furthermore, it is recognized that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. If Phase II testing was required in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. *See* In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436 (Fed. Cir. 1995); MPEP § 2107.01(III).

The identification of the claimed peptides showing differential expression in Type II diabetes relative to healthy control patients puts researcher one step closer to understanding the pathogenesis of Type II diabetes and thus, also one step closer to improved diagnosis and treatment of Type II diabetes. The mass spectral profiles of the claimed peptides can be used immediately to screen patient populations for links to Type II diabetes or the peptides can be used in further research to improve diagnosis and

treatment of Type II diabetes. There is no question that improved diagnosis and treatment of Type II diabetes provides a tangible benefit to society; especially for the population susceptible to the development of Type II diabetes. Since the claimed peptides (SEQ ID NOS:1 and 4) have a "real-world" use in their currently available form as markers for Type II diabetes, i.e. the mass spectral profiles can be used to screen patient populations, the claimed peptides thus have a substantial utility.

Accordingly, there is a critical distinction between an invention that can be used in further experimentation and research, and an invention that requires further experimentation and research before it can be used. Applicants respectfully submit that the Examiner has erroneously found the claimed invention to be the latter rather than the former.

The Examiner cites Fisher in rejecting claim 1 and attempts to draw a parallel to the instant application by asserting that, just as in Fisher - where the Board reasoned that the use of the claimed expressed sequence tags ("ESTs") for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," Fisher, 421 F.3d at 1368 - the detection of the claimed peptides in a sample of a patient suspected of having Type II diabetes provides no meaningful information as to the "link" or diagnosis determination. *See* page 11 of the Final Rejection mailed on March 16, 2006.

Applicants respectfully submit that the facts in Fisher are inapposite to those concerning the present application. Fisher's invention related to five purified nucleic

acid sequences – ESTs - obtained from the leaf tissue of maize plants. As described in Fisher, an EST is a short nucleotide sequence that represents a fragment of a cDNA clone. It is typically generated by isolating a cDNA clone and sequencing a small number of nucleotides located at one end of the two cDNA strands. When an EST is introduced into a sample containing a mixture of DNA, the EST may hybridize with a portion of the DNA. Such binding shows that the gene corresponding to the EST was being expressed at the time of mRNA extraction.

Fisher disclosed in his application that the claimed ESTs may have been used in a variety of ways, including, for example, measuring the level of mRNA in a tissue sample via microarray technology to provide information about gene expression, isolating promoters and identifying the presence or absence of a polymorphism. Fisher, 421 F.3d at 1368. However, Fisher made no disclosure regarding the precise structure or function of either the genes or the proteins encoded for by those genes to which the claimed ESTs correspond. Id.

The Examiner of the Fisher application rejected the claims for lack of utility under 35 U.S.C. § 101 and lack of enablement under 35 U.S.C. § 112, first paragraph. The Board affirmed the rejections. In upholding the rejection, the Court cited the guidelines in MPEP § 2107.01(I) that state a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. The Court noted the Applicants' admission that the underlying genes had no known functions, and that "[e]ssentially, the claimed ESTs act as no more than research intermediaries that may help scientists to isolate the particular underlying protein-encoding genes and conduct

further experimentation on those genes". Id., at 1373. Accordingly, the Court found the ESTs to be mere "objects of use-testing", upon which scientific research could be performed with no assurance that anything useful will be discovered in the end. Id., *citing* Brenner, 383 U.S. at 535. Fisher's asserted uses represented merely hypothetical possibilities, objectives which the claimed ESTs, or any other EST for that matter, could possibly achieve, but none for which they have been used in the real world. For example, Fisher asserted that the ESTs could be used to identify polymorphisms or to isolate promoters. Nevertheless, in the face of a utility rejection, Fisher did not present any evidence showing that the ESTs had been used in either way. Id. Since nothing was known about the genes or proteins corresponding to the claimed ESTs, nothing set the claimed ESTs apart from the more than 32,000 ESTs disclosed in the application or from any EST derived from any organism. Id., at 1374. In other words, any EST could be used to isolate any promoter. Furthermore, the use of the ESTs to actually identify the associated gene would constitute significant further experimentation, rendering the ESTs unable to be used in their current form. Ultimately, Fisher's ESTs were deemed only to be research intermediaries in the identification of underlying protein-encoding genes of unknown function. Id., at 1373.

In contrast to the invention of Fisher, the peptides (SEQ ID NOS: 1 and 4) of the instant invention are known to be fragments of fibronectin precursor protein having the amino acid sequence (i.e. structure) VDVIPVNLPGEHGQR (SEQ ID NO:1) and RVDVIPVNLPGEHGQRL (SEQ ID NO:4) . Furthermore, the claimed peptides are disclosed as markers of a specific disease condition, Type II diabetes. Any skilled artisan, without significant further research, could utilize the mass spectral profiles of the claimed

peptides, shown in Figures 2 and 4, as references for comparison with mass spectral profiles obtained from an unknown sample to screen the sample for a link to Type II diabetes through comparison of expression patterns.

Thus, Applicants respectfully submit that the Examiner's attempt to draw a parallel between Fisher and the instant application fails to support her finding a lack of specific and substantial utility, as the facts in Fisher are not akin to the instant application.

It is clear, from consideration of all of the foregoing remarks, that the claimed invention has a specific and substantial utility. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* showing for lack of specific and substantial utility.

2. *The Examiner Improperly Finds Applicant's Asserted Utility Lacking in Credibility*

The Examiner does not doubt or dispute the results of differential expression of the instant claimed peptides of SEQ ID NOS:1 and 4. The main point of disagreement appears to be the interpretation of these results and what constitutes a specific, substantial and credible utility. *See* page 8 of the Final Rejection mailed on March 16, 2006. Thus, the Examiner appears to believe that the showing of differential expression of the claimed peptides in Type II diabetes as compared to expression in healthy controls is not sufficient to indicate that the claimed peptides could be used as markers for Type II diabetes.

Applicants note that it is improper for Office personnel to merely question operability. Factual reasons must be set forth which would lead one of skill in the art to question the objective truth of the statement of operability. MPEP § 2107.02(IV).

The Examiner provides her opinion on what one of skill in the art would know in several parts of the rejection. For example, at page 10 of the Final Office Action mailed on March 16, 2006, the Examiner states that one skilled in the art readily appreciates that detection of differentially expressed proteins represents only the first step in identification of molecules that have a diagnostic potential and at page 11, that one skilled in the art readily appreciates that many proteins are differentially expressed between healthy and "diseased" tissues (cancer cells, for example, overexpress a plurality of proteins by virtue of uncontrolled proliferation); however, not all of these proteins constitute biomarkers, as molecules that allow to distinguish disease vs. healthy state. However, nowhere does the Examiner provide reasoning or references evidencing why one of skill in the art would "readily appreciate" these things.

Furthermore, the Examiner requires Applicant to provide complete characterization of the claimed peptides (pages 10 and 11 of the Final Office Action mailed on March 16, 2006), including data indicating what level of differential expression of the claimed peptides is diagnostic of Type II diabetes (page 10 of the Final Office Action mailed on March 16, 2006), to establish a utility for the claimed peptide.

The instant situation is akin to that in Cortright. Cortright's invention was drawn to a method for treating baldness by applying Bag Balm (a commercially available product used to soften cow udders) to human scalp. The Examiner of the Cortright application rejected the claim drawn to this invention under 35 U.S.C. § 101 as lacking

utility. According to the Examiner, Cortright's statement of utility, i.e. her claims of treating baldness, were not credible because baldness was generally accepted in the art as being incurable. The Examiner therefore required clinical evidence to establish the claimed utility, which Cortright did not supply. Cortright, 165 F.3d at 1355.

The Board reversed the rejection under 35 U.S.C. § 101 because the Examiner did not set out sufficient reasons for finding Cortright's statements of utility incredible. The Board additionally noted that there is no per se requirement for clinical evidence to establish the utility of any invention. Id.

Applicants respectfully submit that the Examiner has similarly erred by improperly questioning the operability of the invention, in that she states what one of skill in the art would believe without providing evidence to support her conclusion. Additionally, Applicants respectfully submit that the Examiner has further erred by requiring Applicants to provide "complete characterization" of the claimed peptide in order to establish utility since precedent dictates that evidence of absolute certainty is not required.

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 US 835 (1984); MPEP §2107.02(III)(A). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e. "question") the truth of the statement of utility. MPEP § 2107.02(III)(A). Alternatively, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. MPEP § 2164.07(I)(C).

Furthermore, an Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill in the art would not believe the applicants' assertion of utility. Brana, 51 F.3d at 1568; MPEP § 2107.01(III).

In the prior art, the showing of a link between a peptide and a disease implies the potential for use of the peptide for diagnosis and/or therapeutics of the disease. *See* page 18 of the Response filed on February 9, 2006. For example, Blennow et al. (Dementia 6(6):306-311 1995, attached to the Response filed on February 9, 2006 and labeled as reference #5) suggest, based upon differential expression, that chromogranin in cerebrospinal fluid has a potential as a biochemical marker in Alzheimer's disease (Type I, pure AD). Since these practices are common, it is reasonable to believe that when one of skill in the art observes the differential expression of the claimed peptides between Type II diabetes patients and healthy control patients; one of skill in the art would, more likely than not, connect these peptides with potential diagnostics and/or therapeutics for Type II diabetes.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptides (SEQ ID NOS:1 and 4), fibronectin, and Type II diabetes to be reasonable because there is a known association between fibronectin and Type II diabetes.

Fibronectin is a key component of the extracellular matrix; functioning, through a series of binding domains, to maintain normal cell morphology via organization of cell attachment to the extracellular matrix. Fibronectin is particularly prone to fragmentation since the regions between the binding domains are highly susceptible to proteolysis. Fibronection fragments are known to have functions not found in the intact protein, such

as exerting affects on the proliferation and migration of endothelial cells. *See* pages 12 and 13 of the Response filed on February 9, 2006 and the article of Grant et al. Diabetes 47:1335-1340 1998 (labeled as reference 1) attached thereto.

Additionally, increased proteolysis is known to contribute to the pathologic process of Type II diabetes. *See* page 13 of the Response filed on February 9, 2006 and comment by Luc Tappy on Gastadelli et al. Diabetes 49:1367-1373 2000 (labeled reference 2) attached thereto.

Furthermore, excess fibronectin produced in diabetes is theorized to be available for fragmentation. Grant et al. hypothesized that the formation of abnormal fibronectin fragments *in vivo* could facilitate aberrant angiogenesis, as seen in such conditions as proliferative diabetic retinopathy. *See* page 13 of the Response filed on February 9, 2006 and the article of Grant et al. Diabetes 47:1335-1340 1998 (labeled as reference 1) attached thereto.

The claimed peptides (SEQ ID NOS:1 and 4), elucidated from and differentially expressed in diseased versus normal samples, are identified as fragments of fibronectin precursor protein at page 46, line 14 to page 47, line 2 of the specification as originally filed and are consistently replicated in the sample population. The gels shown in Figures 1 and 3 demonstrate that these peptides are found to be expressed in normal patients but absent in Type II diabetes patients. This data is consistent with the studies indicating the involvement of fibronectin in the pathogenesis of diabetes. Thus, the instant inventors hypothesized that expression of the fibronectin precursor fragments in patients considered to be normal with regard to Type II diabetes when compared to expression seen in patients with a history of Type II diabetes indicates that fragmentation of fibronection

may occur during the diabetic disease process. One of skill in the art, considering the known association of fibronectin and diabetes, would find such a hypothesis to be reasonable.

Considering that there is a known increase in proteolysis in Type II diabetes and that fibronectin is particularly sensitive to such proteolysis (degradation into fragments) and further considering the suggestion in the prior art that fibronectin fragments may be involved in pathogenic diabetic processes such as proliferative retinopathy, a skilled artisan would find Applicants' hypothesis and the data disclosed in the specification entirely plausible, and thus would reasonably link the claimed peptides (SEQ ID NOS:1 and 4) with Type II diabetes.

One of ordinary skill in the art would conclude, based upon all of the foregoing remarks, that the asserted utility for the claimed peptides, use as markers for Type II diabetes, is more likely than not true. Thus, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case for lack of credible utility.

B. The Examiner Erred in Rejecting Claim 1 under 35 U.S.C. § 112, First Paragraph.

1. The Examiner Improperly Finds the Invention Nonenabled

Claim 1, as presented in the Response filed on February 9, 2006, stands finally rejected (Final Rejection dated March 16, 2006) under 35 USC § 112, first paragraph.

It is well established that the enablement requirement of 35 U.S.C. § 112 incorporates the utility requirement of 35 U.S.C. § 101. Fisher, 421 F.3d at 1378. Where a written description fails to illuminate a credible utility, the PTO will make both a Section 112 rejection for failure to teach how to use the invention and a Section 101

rejection for lack of utility. Cortright, 165 F.3d at 1355. "If [certain] compositions are in fact useless, [a] specification cannot have taught how to use them." Id..

In most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101. As the Court of Customs and Patent Appeals stated in In re Langer:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope. Langer, 503 F.2d at 1391 (emphasis in original).

The "Langer" test for utility has been used in evaluation of rejections under 35 U.S.C. § 112, first paragraph, where the rejection is based on a deficiency under 35 U.S.C. § 101. An examiner cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description. Cortright, 165 F.3d at 1357. A reason to doubt an asserted utility may be established when the description "suggests an inherently unbelievable undertaking or involves implausible scientific principles." Brana, 51 F.3d at 1566.

In the present application, the Examiner rejects Claim 1 under 35 U.S.C. § 112, first paragraph, "since the claimed invention is not supported by either a clear asserted utility or well established utility for the reasons set forth [in the Examiner's rejection under 35 U.S.C. § 101] . . . one skilled in the art clearly would not know how to use the claimed invention." Applicants respectfully request reconsideration of the rejection as Applicants have established in the above remarks that the claimed invention has a specific and substantial credible utility.

A skilled artisan could easily follow the methodology for elucidating the presence of the claimed peptides (SEQ ID NOS: 1 and 4), as disclosed in the patent application (and reiterated *supra*), on a non-differentiated patient population, in order to discern members of the population who manifest Type II diabetes.

Thus, one of skill in the art clearly would know how to use the claimed peptides (SEQ ID NOS: 1 and 4) as markers for Type II diabetes. Thus, Applicants respectfully submit that the Examiner has failed to properly establish lack of enablement.

IX. APPENDIX

The claim involved in this Appeal, Claim 1, is attached hereto as forms the Appendix.

X. CONCLUSION

In light of the foregoing, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for lack of utility and lack of enablement in the present application. Favorable reconsideration of this application and withdrawal of the rejections of claim 1 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph is courteously requested.

APPENDIX

Claim 1. An isolated biopolymer marker which evidences a link to Type II diabetes selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:4.